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NOVEL 4-DIPHENYLMETHYL PIPERIDINE DERIVATIVES

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BACKGROUND OF THE INVENTION

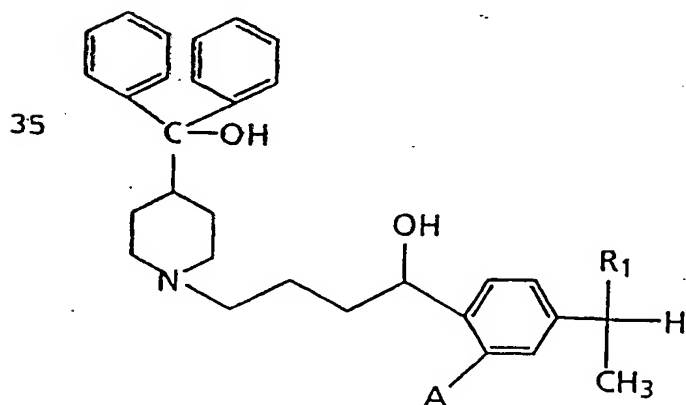
This invention relates to novel diphenylmethyl piperidine derivatives. More particularly, this invention relates to 4-diphenylmethyl piperidinobutanol derivatives which are useful as antihistamines, antiallergy agents and bronchodilators.

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SUMMARY OF THE INVENTION

More specifically this invention relates to compounds of formula (I)



wherein R_1 is $-CH_3$, $-CH_2OH$, $-COOH$ or $-COO-(C_{1-6})alkyl$;
A is hydrogen or hydroxy,
including the stereoisomers, enantiomers, racemic mixtures thereof or their pharmaceutically acceptable salts thereof.

The present invention further provides a method for treating allergic reactions in a patient in need thereof which comprises administering to said patient an effective

antiallergic or antihistaminic amount of compound of
5 formula (I).

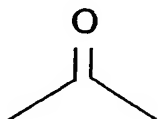
10 As used herein in this application:

(a) the term "alkyl" means univalent radical (-R). It
15 includes the straight and branched chain saturated
aliphatic hydrocarbyl moieties having the indicated number
of carbon atoms. For example, the term "C₁₋₆ alkyl" refers
20 to a saturated straight or branched chain hydrocarbon
radical having from one to six carbon atoms, preferably
having one to four carbon atoms ("C₁₋₄ alkyl") and more
25 preferably having one to three carbon atoms ("C₁₋₃ alkyl").
Included within the scope of this term are methyl, ethyl,
n-propyl, isopropyl, n-butyl, isobutyl, tertiary butyl,
pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, and the
like;

30

(b) the designation -C(O)- or -CO- refers to a carbonyl
group of the formula:

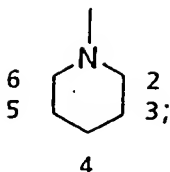
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The term -COOR includes those alkoxycarbonyl moieties
wherein R is H or a C₁₋₆ alkyl moiety or preferably a C₁₋₃
alkyl moiety, embracing, for example, methoxycarbonyl,
ethoxycarbonyl, t-butyloxycarbonyl, and the like. It is
also understood that an alkoxycarbonyl wherein R is other
than H is also referred to as an ester;

5

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(d) the term "halo" refers to a halogen such as a fluorine atom a chlorine atom or a bromine atom, or a iodine atom.

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The term "pharmaceutically acceptable salts" include those acid addition salts derived by reaction with acids, for example, hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acids and such organic carboxylic acids as acetic, propionic, glycolic, maleic, tartaric, citric, salicylic, 2-acetyloxybenzoic acids or organic sulfonic acids such as methanesulfonic, 4-toluenesulfonic and naphthalenesulfonic acids. Of course other acids well known to the pharmaceutical art may also be utilized. The term "pharmaceutically acceptable salts" may also include hydrates.

35

Stereoisomers of the compounds of formula (I) is a general term for all isomers of these compounds that differ only in the orientation of their atoms in space. It includes geometric (*cis/trans*) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers or diastereoisomers). The term "enantiomer" refers to two stereoisomers that are mirror images of one another and not identical, not being superposable. The term "chiral center" refers to a carbon atom to which four different groups are attached. The nomenclature R/S is used as described in IUPAC-IUB Joint Commission on Biochemical Nomenclature, *Eur. J. Biochem.* 138: 9-37 (1984). A chiral material may either contain an equal amount of the R and S isomers in which case it is called "racemic mixture" or it may not contain equal amounts of R and S isomer in which

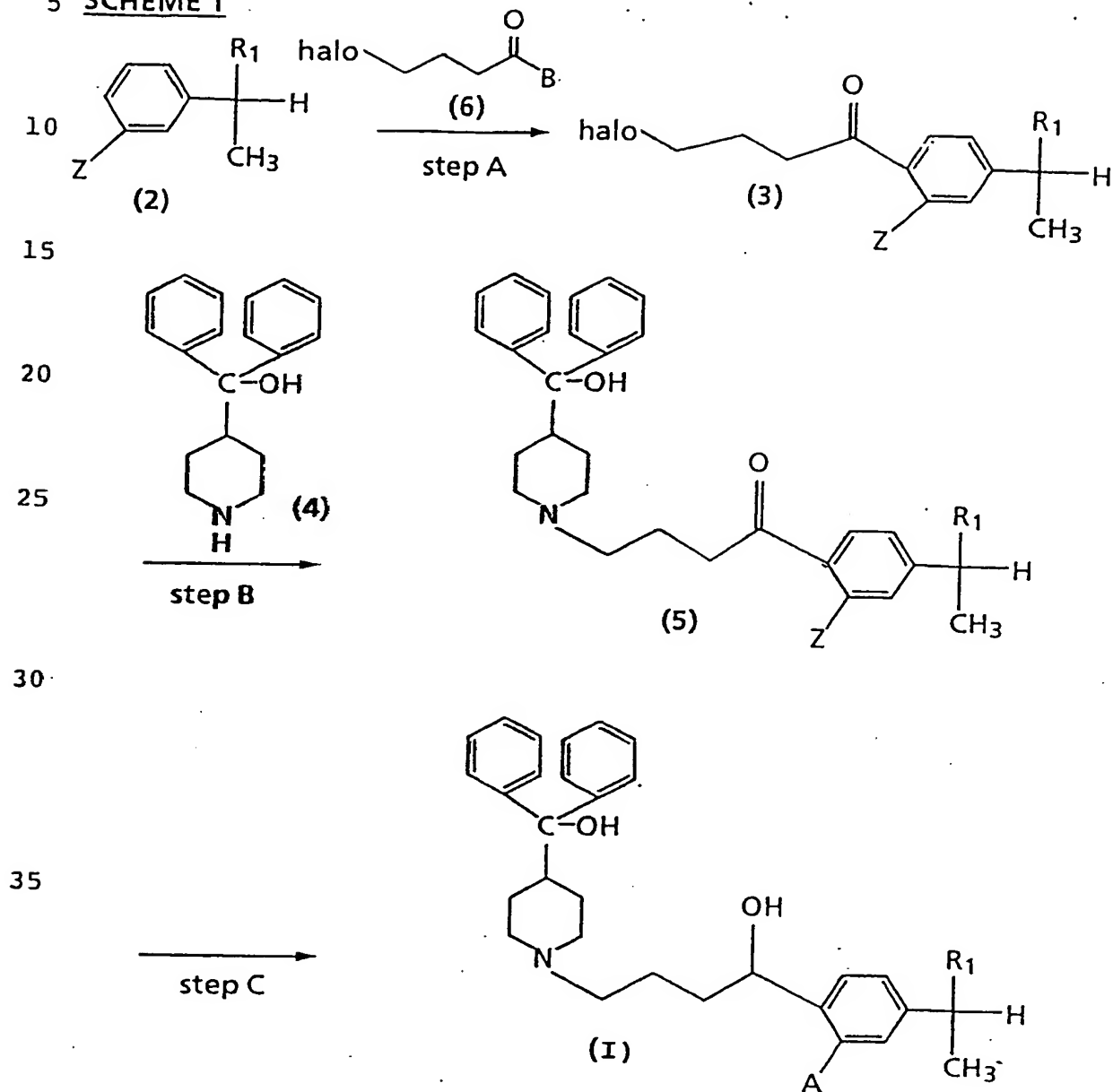
case it is called "optically active", or "nonracemic
5 mixture". A mixture may be resolved or isolated according
to conventional and standard procedures well known in the
art, e.g., chromatographic separation on chiral stationary
10 phase, use of optically active esters, fractional
crystallization of addition salts formed by reagents used
for that purpose, as described in "Enantiomers, Racemates,
15 and resolutions", J. Jacques, A. Collet, and S.H. Wilen,
Wiley (1981), enzymatic resolution and the like.
Stereoisomer resolution is carried out on the
20 intermediates, or the final products of formula (I). The
term "resolution" means separation of a racemic mixture
into its optically active components. In addition,
25 enantiomers may be prepared by utilizing enantioselective
or asymmetric synthesis which are well known by a person of
ordinary skill in the art. The term "enantioselective" or
"asymmetric" means the ability to produce a product in an
optically active form.

30

It is understood that the compounds of formula (I) may
exist in a variety of stereoisomeric configurations. It is
further understood that the compounds of the present
invention encompass those compounds of formula (I) in each
35 of their various structural and stereoisomeric
configurations as individual isomers or as mixtures of
isomers.

The compounds of this invention are prepared by various
means, and certain compounds of the invention are employed
to prepare other compounds of the invention.

The compounds of the formula (I) may be synthesized by
one with ordinary skill in the art using the procedures as
more fully described in the following United States Patent
No. 4,254,129 issued March 3, 1981 and United States Patent
No. 4,254,130 issued March 3, 1981 which are incorporated
herein by reference.

5 SCHEME 1

Step A: Friedel Crafts acylation; Step B: Alkylation; Step C: Reduction.

SCHEME 1

Generally, the compounds of formula (I) wherein R₁ is -CH₃, -COOH, or -COO-(C₁₋₆ alkyl) may be synthesized following the general scheme 1.

Step A

5

10 The ω -halo phenylbutanone derivative of structure (3), wherein Z is hydrogen, hydroxy or a protected hydroxy, may be prepared by reacting an appropriate phenyl derivative of formula (2), wherein Z is hydrogen, hydroxy or a protected hydroxy, with an appropriate ω -halo compound of the

15 structure (6) halo-(CH₂)₃-C(=O)-B, wherein B is halo or hydroxy, halo is Cl, Br or I, which is known in the art or prepared by procedures well known in the art, under general conditions of a Friedel Crafts acylation as disclosed in

20 *Methoden der Organischen Chemie* (Houden-Weyl, VII/2a teil I, 1973); or in *Friedel-Crafts and related reactions* (Interscience, New York, 1963-1964), which are incorporated herein by

25 reference. The reaction is carried out most commonly in a solvent such as methylene chloride, dichloroethane, tetrachloroethane, chlorobenzene, nitromethane, 1-nitropropane, diethyl ether, acetonitrile, n-hexane or

30 carbon disulfide or without any solvent in the presence of a suitable Lewis acid such as ferric chloride, iodine, zinc chloride, aluminum chloride and iron. More preferably the reaction is carried out using methylene chloride as solvent and aluminum chloride or ferric chloride as catalyst. The

35 reaction time varies from 1/2 hour to 25 hours, preferably 4 to 10 hours and the reaction temperature varies from -15 °C to 100 °C, preferably from -10 °C to 20 °C. The corresponding ω -halo phenylbutanone derivative of structure (3) is recovered from the reaction zone by an aqueous quench followed by extraction as known in the art. The ω -halo phenylbutanone derivative of structure (3) may be purified by procedures well known in the art, such as crystallization and/or distillation.

Step B

5

The diphenylmethyl piperidine oxobutyl derivative of formula (5) is obtained by alkylation of 4(α,α -diphenyl) piperidine methanol of formula (4) with an ω -haloalkyl phenylbutanone derivative of formula (3) wherein halo is Cl, Br or I and Z is hydrogen or hydroxy or protected hydroxy as described in United States Patent No. 4,254,130. The alkylation reaction is carried out in a suitable solvent, preferably in the presence of a suitable non-nucleophilic base and optionally in the presence of a catalytic amount of an iodide source, such as potassium or sodium iodide. The reaction time varies from about 4 to 120 hours and the reaction temperature varies from about 40°C to the reflux temperature of the solvent. Suitable solvents for the alkylation reaction include alcohol solvents such as, methanol, ethanol, isopropyl alcohol, or n-butanol; ketone solvents, such as, cyclohexanone, methyl isobutyl ketone; hydrocarbon solvents, such as, benzene, toluene or xylenes; halogenated hydrocarbons, such as, chlorobenzene or methylene chloride or dimethylformamide. More preferably a mixture of water and hydrocarbon solvents, such as xylenes, is used. Suitable non-nucleophilic bases for the alkylation reaction include inorganic bases, for example, sodium bicarbonate, potassium carbonate, or potassium bicarbonate or organic bases, such as, a trialkylamine, for example, triethylamine or pyridine, or an excess of 4(α,α -diphenyl) piperidine-methanol of formula (4) may be used.

The desired compound of formula (I) may be prepared in one step by reduction of the so-produced ketone (5) or in two steps by reduction of the ketone (5) followed by base hydrolysis, or in two steps by base hydrolysis followed by reduction of the ketone (5), depending on the compound desired and the reducing agent employed as disclosed in United States Patent No. 4,285,957.

5 For example, reduction of the appropriate diphenyl-
methyl piperidine oxobutyl derivative of structure (5)
wherein R_1 is $-CH_3$ or $-COO-(C_{1-6} \text{ alkyl})$, using, for example,
10 a suitable reducing agent such as sodium borohydride,
potassium borohydride, sodium cyanoborohydride, or
tetramethylammonium borohydride is carried out in lower
15 alcohol solvents, such as, methanol, ethanol, isopropyl
alcohol or n-butanol, or in aqueous lower alcohol
solutions, at temperatures ranging from about $0^\circ C$ to the
20 reflux temperature of the solvent, and the reaction time
varies from about 1/2 hour to 8 hours. Preferably, the
reaction is carried out using sodium borohydride or
25 potassium borohydride as reducing agent, in presence of
sodium hydroxide in an aqueous solution of alcohol such as
methanol or ethanol. Other suitable reducing agents are,
for example, lithium tri-tert-butylaluminumhydride and
diisobutylaluminum hydride. These reduction reactions are
30 carried out in suitable solvents diethyl ether,
tetrahydrofuran or dioxane at temperatures ranging from
about $0^\circ C$ to the reflux temperature of the solvent, and the
reaction time varies from about 1/2 hour to 8 hours.

35 Catalytic reduction may also be employed in the
preparation of appropriate diphenylmethyl piperidine
derivative of structure (I) wherein R_1 is $-CH_3$ or
 $-COO-(C_{1-6} \text{ alkyl})$ from an appropriate diphenylmethyl
piperidine oxobutyl derivative of structure (5) wherein R_1
is $-CH_3$ or $COO-(C_{1-6} \text{ alkyl})$, using hydrogen gas in the
presence of a suitable catalyst such as Raney nickel,
palladium, platinum or rhodium catalysts in lower alcohol
solvents, such as, methanol, ethanol, isopropyl alcohol or
n-butanol or acetic acid or their aqueous mixtures, or by
the use of aluminum isopropoxide in isopropyl alcohol.

Reduction using sodium borohydride or potassium borohydride is preferred over catalytic reduction for those diphenylmethyl piperidine derivatives of structure (I) wherein R_1 is $-CH_3$ or $-COO-(C_{1-6} \text{ alkyl})$.

In addition, a chiral reduction of the appropriate diphenylmethyl piperidine oxobutyl derivative of structure (5) wherein R_1 is $-CH_3$ or $-COO-(C_{1-6} \text{ alkyl})$, using, for example, (+) or (-)-B-chlorodiisopinocampheylborane gives the corresponding (R) or (S)-diphenylmethyl piperidine derivative of structure (I) wherein R_1 is $-CH_3$ or $-COO-(C_{1-6} \text{ alkyl})$. Other suitable chiral reducing agents are, (R) and (S)-oxazaborolidine/ BH_3 , potassium 9-O-(1,2:5,6-di-O-isopropylidene- α -D-glucofuransoyl)-9-boratabicyclo[3.3.1]nonane, (R) and (S)-B-3-pinanyl-9-borabicyclo[3.3.1]nonane, NB-Enantride, Lithium (R)-(+ and (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl alkoxyl aluminum hydride, (R)-(+ and (S)-(-)-2,2'-dihydroxy-6,6'-dimethylbiphenyl borane-amine complex, tris([(1S,2S,5R)-2-isopropyl-5-methyl-cyclohex-1-yl]methyl)aluminum, [(1R,3R)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium chloride, (R)-BINAP-ruthenium complex/ H_2 and 6,6'-bis(diphenylphosphino)-3,3'-dimethoxy-2,2',4,4'-tetramethyl-1,1'-biphenyl.

The compounds wherein R_1 is $-COO-(C_{1-6} \text{ alkyl})$ may be hydrolyzed by treatment with an inorganic base to give the corresponding diphenylmethyl piperidine derivative of formula (I) R_1 is $-COOH$.

For example, hydrolysis may be achieved by using a suitable non-nucleophilic base, such as sodium methoxide in methanol as is known in the art. Other methods known in the art for ester cleavage include potassium carbonate in methanol, methanolic ammonia, potassium carbonate, potassium hydroxide, calcium hydroxide, sodium hydroxide, magnesium hydroxide, sodium hydroxide/pyridine in methanol,

potassium cyanide in ethanol and sodium hydroxide in
5 aqueous alcohols, with potassium hydroxide being preferred.
The reaction is typically carried out in an aqueous lower
alcohol solvent, such as methanol, ethanol, isopropyl
10 alcohol, n-butanol, 2-ethoxyethanol or ethylene glycol or
pyridine, at temperatures ranging from room temperature to
the reflux temperature of the solvent, and the reaction
15 time varies from about 1/2 hour to 100 hours.

The diphenylmethyl piperidine derivative of formula (I)
20 wherein R_1 is $-CH_2OH$ may be prepared by reducing the
corresponding derivative wherein R_1 is $-COOH$ or $-COO-(C_{1-6}$
alkyl).

25 For example, reduction of the appropriate diphenyl-
methyl piperidine oxobutyl derivative of structure (5)
wherein R_1 is $-CH_2OH$, using, for example, a suitable
reducing agent such as lithium aluminum hydride or diborane
30 is carried out in ether solvents such as, for example,
diethyl ether, tetrahydrofuran or dioxane at temperatures
ranging from about $0^\circ C$ to the reflux temperature of the
solvent, and the reaction time varies from about 1/2 hour
to 8 hours.

35 In addition, the individual (R) and (S) isomers of the
diphenylmethyl piperidine derivative of formula (I) can be
prepared by techniques and procedures well known and
appreciated by one of ordinary skill in the art.

For example, the mixture of (R) and (S) isomers of the
diphenylmethyl piperidine derivative of formula (I) may be
subjected to chiral chromatography to give the
corresponding individual (R)-diphenylmethyl piperidine
derivative of formula (I) and (S)-diphenylmethyl piperidine
derivative of formula (I).

In addition, the individual (R) and (S) isomers of the
5 diphenylmethyl piperidine oxobutyl derivative of formula
(5) and the diphenylmethyl piperidine derivative of formula
(I) can be prepared by techniques and procedures well known
10 and appreciated by one of ordinary skill in the art and
described in "Enantiomers, Racemates, and Resolutions",
Jacques, Collet and Wilen, Wiley (1981).

15
One such method involves reacting the mixture of (R)
and (S) isomers of the diphenylmethyl piperidine derivative
20 of formula (I) with appropriate chiral acids to give the
corresponding mixture of diastereomeric acid addition
salts. The individual (R)-chiral acid addition salts of
25 the diphenylmethyl piperidine compound of structure (I) and
(S)-chiral acid addition salts of the diphenylmethyl
piperidine compound of structure (I) are obtained by
recrystallization and the individual chiral (R)-
diphenylmethyl piperidine compound of structure (I) and
30 chiral (S)-diphenylmethyl piperidine compound of structure
(I) are obtained by subjecting the individual (R)-chiral
acid addition salts of the diphenylmethyl piperidine
compound of structure (I) and (S)-chiral acid addition
salts of the diphenylmethyl piperidine compound of
35 structure (I) to base in order to free the piperidine
nitrogen from the acid addition complex. Examples of
suitable chiral acids are tartaric acid (+), (-), O,O'-
dibenzoyltartaric acid (+), (-), O,O'-di-p-toluyltartaric
acid (+), (-), 2-Nitrotartranillic acid (+), (-), mandelic
acid (+), (-), malic acid (+), (-), 2-phenoxypropionic acid
(+), hydratropic acid (+), (-), N-acetylleucine (-), (+),
N-(α -methylbenzyl)succinamide (+), (-), N-(α -methylbenzyl)-
phthalamic acid (+), (-), camphor-10-sulfonic acid (+), 3-
bromocamphor-9-sulfonic acid (+), (-), camphor-3-sulfonic
acid (+), quinic acid (+), (-), Di-O-isopropylidene-2-oxo-
L-gulonic acid (-), Lasalocid (-), 1,1'-binaphthyl-2,2'-
phosphoric acid (+), (-), chloestenonesulfonic acid.

5 In addition, the individual (R) and (S) isomers of the
diphenylmethyl piperidine derivative of formula (I) can be
prepared by reacting the mixture of (R) and (S) isomers of
10 the diphenylmethyl piperidine derivative of formula (I)
with appropriate organic chiral acids to give the
corresponding mixture of diastereomeric acid esters. The
15 individual chiral ester of (R)-diphenylmethyl piperidine
compound of structure (I) and chiral ester of (S)-
diphenylmethyl piperidine compound of structure (I) are
20 obtained by recrystallization or chromatography and the
individual chiral (R)-diphenylmethyl piperidine compound of
structure (I) and chiral (S)-diphenylmethyl piperidine
25 compound of structure (I) are obtained by subjecting chiral
ester of (R)-diphenylmethyl piperidine compound of
structure (I) and chiral ester of (S)-diphenylmethyl
piperidine compound of structure (I) to hydrolysis
conditions.

30

It is understood that each hydroxy group in the
compounds described in this invention are optionally
protected or unprotected. The selection of and utilization
of suitable protecting groups is well known by one with
35 ordinary skill in the art and is described in "Protective
Groups In Organic Chemistry", Theodora W. Greene, Wiley
(1981) which is herein incorporated by reference. For
example, suitable protecting group for those hydroxy
functionalities present include ethers such as methyl
ether, cyclohexyl ether, isopropyl ether, t-butyl ether, or
methoxymethyl ether, tetrahydropyranyl, tetrahydrothio-
furanyl, 2-phenylselenylethyl ether, o-nitrobenzyl ether,
trimethylsilyl ether, t-butyldiphenylsilyl ether,
tribenzylsilyl ether, isopropyl dimethylsilyl ether, t-
butyldimethyl silyl ether, t-butyldiphenylsilyl ether,
tribenzylsilyl ether, triisopropylsilyl ether; and ester,
such as acetate ester, levulinate ester ($\text{CH}_3\text{COCH}_2\text{CH}_2\text{CO}_2^-$),
pivaloate ester

5 ((CH₃)₃CCO₂-), benzoate ester, 2,4,6,-trimethylbenzoate
(mesitoate) ester, methyl carbonate, p-nitrophenyl
carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate
and N-phenylcarbamate, phosphinates such as dimethyl-
10 phosphonyl ester ((CH₃)₂P(O)O-), sulfonates such as methyl-
sulfonate or mesyl (-OSO₂CH₃) or toluene sulfonate or tosyl
(-OSO₂C₆H₄-p-CH₃).

15

The 4(α,α-diphenyl) piperidine methanol of structure
(4) is readily available to one with ordinary skill in the
20 art and is described in United States Patent No. 4,254,129,
March 3, 1981, United States Patent No. 4,254,130, March 3,
1981, United States Patent No. 4,285,958, April 25, 1981
25 and United States Patent No. 4,550,116, Oct. 29, 1985.

The derivatives of formula (2) are commercially
available or readily prepared by one with ordinary skill in
the art.

30

Alternatively, one with ordinary skill in the art may
synthesize the compounds of formula (I) by using the
procedures disclosed in the PCT application WO93/21156
published October 28, 1993 or in the PCT application
35 WO95/00480 published January 5, 1995 which are herein
incorporated by reference.

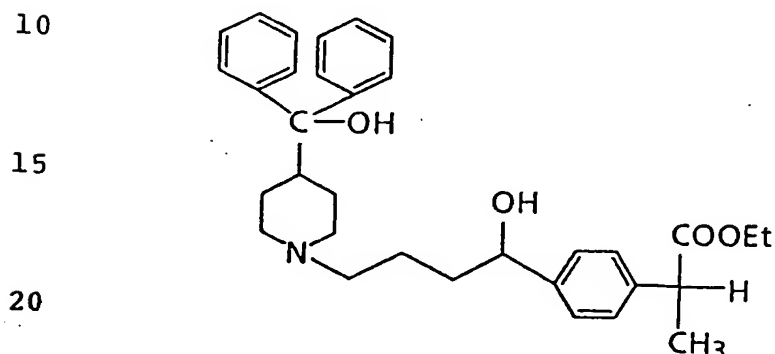
The following examples present typical syntheses as
5 described in Scheme 1. These examples are understood to be
illustrative only and are not intended to limit the scope
of the present invention in any way. As used herein, the
10 following terms have the indicated meanings: "g" refers to
grams; "mmol" refers to millimoles; "mL" refers to
milliliters; "bp" refers to boiling point; "mp" refers to
15 melting point; "°C" refers to degrees Celsius; "Pa" refers
to pascals; "µL" refers to microliters; "µg" refers to
micrograms; and "µM" refers to micromolar; "TLC" refers to
20 thin layer chromatography; "M" refers to molarity; "N"
refers to normal, " $[\alpha]_D^{20}$ " refers to specific rotation of
the D line of sodium at 20 °C obtained in a 1 decimeter
25 cell; "GC" refers to gas chromatography; "R_f" refers to
retention factor and "RPM" refers to revolutions per
minute.

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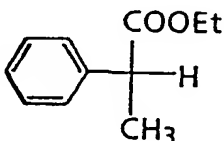
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EXAMPLE 1

5 ETHYL 4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-HYDROXYBUTYL]- α -METHYLPHENYL ACETATE



25 Step 1: ETHYL 2-PHENYLPROPIONIC ACID ESTER



Load into a round-bottomed flask equipped with a condenser and a magnesium sulfate drying tube on top, 2-phenyl propionic acid (1.51 mol, 226 g), concentrated sulfuric acid (3.32 g, 0.033 mol) and absolute ethanol (1 L). Heat the resulting solution at reflux for 22.5 hours. Concentrate the solution under vacuum to obtain an oil (277 g). Add to the oil one liter of fresh ethanol and heat the resulting solution at reflux for another 19.6 hours. Add to the reaction, at ambient temperature, sodium ethoxide (21 weight percent in ethanol, 30 mL). Then add glacial acetic acid (2 g) in order to establish a slightly acidic pH. Remove the solids from the slurry by suction filtration. Concentrate the filtrate under vacuum on a rotary evaporator. Add heptane (400 mL) to the residue and concentrate this solution under vacuum in order to strip away remaining traces of ethanol to give ethyl 2-phenylpropionic acid ester as an oil (276.7 g).

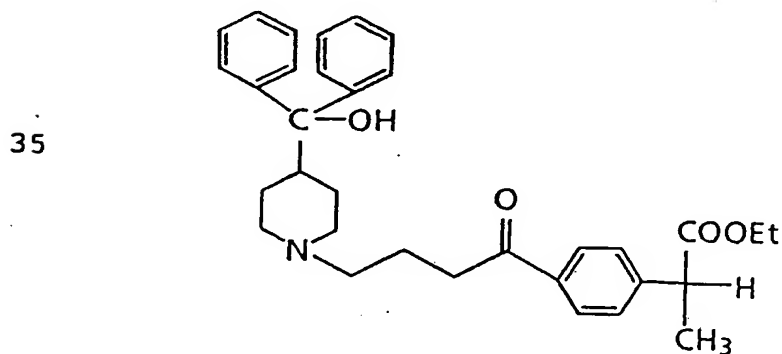
Put the resulting solution into a round-bottomed flask,
5 fitted with an overhead stirrer, a reflux condenser (with
a drying tube on the top) and a gas sparge tube. Sparge
anhydrous hydrogen chloride (22.25 g, 0.61 mol) into the
10 stirred solution. Heat the solution, to 56 °C, over a 3.75
hour period with stirring. Add to the solution at 56 °C
sodium ethoxide (21 weight percent in absolute ethanol; 835
15 g, 2.58 mol sodium ethoxide) over a period of 100 minutes.
Heat the resulting liquid/solid slurry over a period of 15
minutes at 52 °C. Cool the solution to below 20 °C by
20 ice/water bath. Add to the slurry glacial acetic acid
(25.5 mL, 0.445 mol) (pH of an aliquot diluted with an
equal volume of water is 5.0-5.2). Add heptane (250 mL)
25 and allow the slurry to stand at ambient temperature
overnight.

Filter by suction through a pad of filteraid on a
coarse sintered glass funnel. Wash the filtercake with
30 heptane/absolute ethanol (400 mL, 2/1 (v/v)). Concentrate
the combined filtrate and washes on a rotary evaporator up
to 95 °C at 110 mm Hg (14.3 kPa), to obtain brown liquid and
solid residues (433 g). Flash distill the residue through
a bump guard and Claisen head with no rectification at 1 mm
35 Hg vacuum. Collect distillate at overhead temperatures of
40-175 °C to obtain a light yellow oil (346.7 g). Discard
the distillation pot. Purify the so-produced oil as a
mixture of ethyl 3- and 4-(cyclopropylcarbonyl)- α -
methylphenyl acetate by flash distillation under vacuum
through a 1 inch I.D. column, length of 53 inches, packed
with 316 stainless steel High Goodloe 773. Collect the
desired para derivative ethyl 4-(cyclopropylcarbonyl)- α -
methylphenyl acetate (95.9 g) at overhead of 146-147 °C
temperatures.

Put ethyl 4-(cyclopropylcarbonyl)- α -methylphenyl
acetate (73.89 g, 0.300 mol), mixed xylenes (400 mL) and
absolute ethanol (90 mL) into a round-bottomed flask fitted

with an overhead paddle stirrer, a gas sparge tube with
5 fritted end and a reflux condenser with a magnesium sulfate
drying tube. Sparge hydrogen chloride gas from a lecture
bottle (36.68 g, 1.061 mol, anhydrous 99%) into the stirred
10 solution over a period of 15 minutes. Replace the gas
sparge tube with a glass stopper. Heat the solution with
stirring, the temperature rising from 40 °C to 79 °C in 45
15 minutes. Maintain the temperature at 79 °C for another 15
minutes. Replace the reflux condenser with a simple still
head fitted with a condenser and a thermometer. Distill
20 and collect at overhead temperature (80-138 °C). Allow the
yellow solution to cool to ambient temperature and remove
the xylene solvents by rotary evaporation up to 75 °C at
25 12 mm Hg (1.6 kPa) to leave the ethyl 4-(4-chloro-1-
oxobutyl)- α -methylphenyl acetate (87.4 g) as a yellow
solid.

30 Step 3: ETHYL 4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-
PIPERIDINYL]-1-OXOBUTYL]- α -METHYLPHENYL ACETATE



Add ethyl 4-(4-chloro-1-oxobutyl)- α -methylphenyl
acetate (7.6 g, 26.9 mmol) to a solution of 4(α,α -
diphenyl)piperidine methanol (15.8 g, 59.0 mmol) in xylenes
(27 mL) into a single neck round-bottomed flask equipped
with a water-cooled reflux condenser and on the outlet a
calcium sulfate-filled drying tube. Stir and heat the
reaction at 140 °C for 5.5 hours. Cool the slurry reaction
to ambient temperature and add xylenes (15 mL). Heat the
diluted slurry reaction at 50 °C and add glacial acetic acid

(1.52 g, 25.3 mmol). Cool the reaction to ambient
5 temperature and filter by suction. Wash the filtercake
with xylenes (25 mL) and add the filtrate wash to the
original filtrate.

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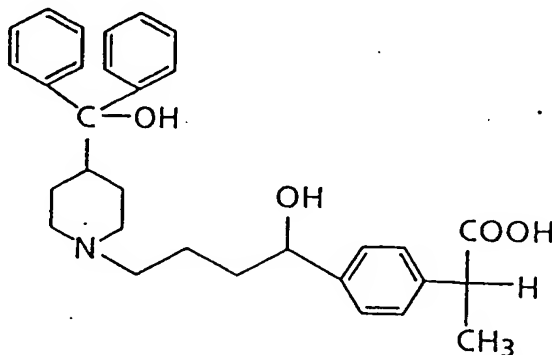
Stir filtrate at ambient temperature and add 37%
aqueous hydrochloric acid (3.02 g, 30.6 mmol) over a 70 min
15 period, to provide a thick solid/liquid slurry. Add to the
slurry absolute 2B ethanol (3 mL) and stir the resulting
slurry for 10 min. Collect the solids by suction
20 filtration, and wash the filtercake with fresh xylenes (20
mL) and heptane (10 mL). Dry the filtercake overnight in a
vacuum oven at 47 °C to obtain 11.05 g of crude ethyl 4-[4-
25 [4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α -
methylphenyl acetate as a light tan solid.

Reduce the so-produced 4-(4-chloro-1-oxobutyl)- α -
methylphenyl acetate following the procedure described in
30 Example 4, step 3 to give the corresponding ethyl 4-(4-
chloro-1-hydroxybutyl)- α -methylphenyl acetate.

EXAMPLE 2

35

4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-
HYDROXYBUTYL]- α -METHYLPHENYL ACETIC ACID



Add ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-
piperidinyl]-1-oxobutyl]- α -methylphenyl acetate (6.00g,
10.5 mmol) to a solution of methanol (30 mL), 50% aqueous

sodium hydroxide (4.30 g, 53.8 mmol) and water (3.5 g).

- 5 Heat under reflux for 1.75 hours. Dissolve the forming solids by addition of water (6 mL). Cool the reaction to 41 °C and add sodium borohydride (0.22 g, 5.82 mmol). Stir
10 the reaction at 40 °C for 1.83 hours. Add acetone (1.65 mL, 22.5 mmol) to the solution and stir at 40 °C for 0.5 hour and overnight at ambient temperature. Heat the solution to
15 32 °C and add 37% aqueous hydrochloric acid (6.66 g, 67.6 mmol) and 5% aqueous hydrochloric acid (7.10 g, 9.7 mmol) in order to reduce the pH of the solution to 2.0.

20

- Add water (24 g) and heat the resulting solution to 37 °C. Cool the solution slowly to -20 °C and collect
25 solids by suction filtration. Wash the filtercake with cold water (10 mL) and dry it at 52 °C for 70 min under vacuum to obtain 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α -methylphenyl acetic acid hydrate as a white solid (5.85 g). Add the so-produced hydrate
30 (5.00 g) to a solution of acetone (15 mL) and water (0.56 g). Stir the mixture at ambient temperature until almost all the solids are dissolved. Filter the solution through a filter aid by suction to obtain a clear solution and rinse with acetone (2 mL). Transfer the filtrate in a
35 single-neck, round-bottomed flask using acetone (13 mL). Stir and heat under reflux. Add ethyl acetate (30 mL) slowly to the refluxing solution, a second liquid phase appears after 12 mL of ethyl acetate has been added. Stir the liquid/liquid mixture at ambient temperature overnight. Reheat the mixture for one hour at reflux and cool to 40 °C. Remove the supernatant solvent phase by pipette. Add fresh acetone (30 mL) and heat the solution under reflux. Add ethyl acetate (30 mL) to the refluxing solution over a 45 min period. Break up the solids by spatula. Heat the resulting slurry under reflux for another hour and then cool to ambient temperature. Collect the solid by suction filtration and wash the the filtercake with ethyl acetate (10 mL). Dry the filtercake in a vacuum oven at 55 °C and

dry open to air overnight to obtain anhydrous 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α -methylphenyl acetic acid as a white solid (3.09 g, 63%).

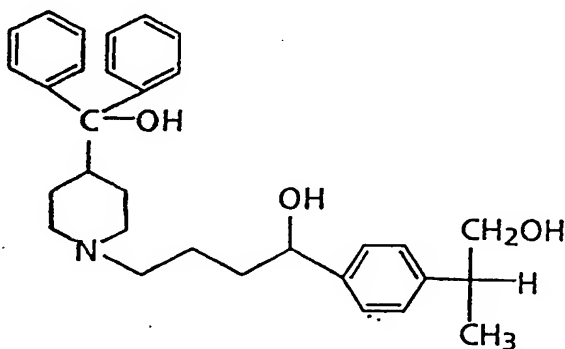
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EXAMPLE 74-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-HYDROXYBUTYL]-2-METHYLPHENETHYL ALCOHOL

15

20

25



30

Add a suspension of ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α -methylphenyl acetate (4 mmol) in tetrahydrofuran (50 mL) slowly to a suspension of lithium aluminium hydride (18 mmol) in tetrahydrofuran (60 mL) under nitrogen atmosphere with stirring. Stir the mixture and heat under reflux for about 3 hours and add tetrahydrofuran (30 mL). Heat under reflux for 4 hours and let stand overnight (about 16 hours). Stir the mixture under a nitrogen atmosphere and add water (2 mL) cautiously followed by an aqueous solution of sodium hydroxide (10 %, 2 mL), water (2 mL) and sodium sulfate (4 g). Warm the mixture to 50-55 °C and stir for 45 minutes, filter and wash the solids and the material with tetrahydrofuran. Combine the filtrates and evaporate under vacuum. Recrystallized the residue from ethanol to give 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-2-methylphenethyl alcohol.

35

EXAMPLES 4, 5 and 6

5

10 ETHYL 4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-
HYDROXYBUTYL]- α -METHYL-3-HYDROXYPHENYL ACETATE, 4-[4-[4-
(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-HYDROXYBUTYL]- α -
METHYL-3-HYDROXYPHENYL ACETIC ACID and 4-[4-[4-
15 (HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-HYDROXYBUTYL]-2-
METHYL-2-(3-HYDROXYPHENYL)-ETHYL ALCOHOL

can be prepared by one ordinary skilled in the art
following the above described examples 1, 2 and 3 but using
20 2-(3-hydroxyphenyl) propionic acid as starting material
instead of 2-phenyl propionic acid. The hydroxy group may
be protected, more preferably methoxymethyl ether group is
25 used.

2-(3-HYDROXYPHENYL) PROPIONIC ACID

30 Ethyl 2-(3-methoxyphenyl) propionic acetate can be
prepared by one with ordinary skill in the art following
the procedure described by Sedgeworth et al. in *J. Chem. Soc.*
Perk T1 (12), 2677-2687 (1985) which is herein incorporated
by reference. Ethyl 2-(3-methoxyphenyl) propionic acetic
35 ester is further deprotected and hydrolyzed according well
known procedures in the art disclosed in "Protective Groups
In organic chemistry" which is herein incorporated by
reference.

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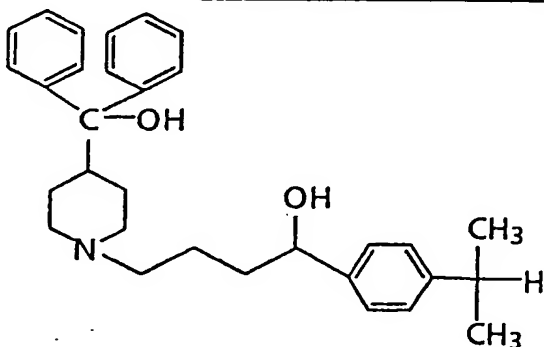
EXAMPLE 7

4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-(4-ISOPROPYLPHENYL) BUTANOL

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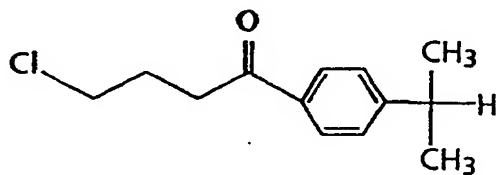
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Step 1: 1-CHLORO-4-(4-ISOPROPYLPHENYL) BUTANONE

25

30



35 Stir aluminium chloride (501.52 g, 3.76 mol) and methylene chloride (1.4 L) in a round-bottomed flask equipped with a nitrogen bubbler. Cool the resulting slurry to -10 °C via ice/ethanol bath. Add 4-chlorobutyl chloride (546.05 g, 3.87 mol) over a period of 45 min so as to keep the temperature of the slurry solution below -3 °C. Cool the resulting solution to -10 °C, and add cumene (477 mL, 3.43 mol) over a period of 80 min, maintaining the temperature of the solution at around -10 °C.

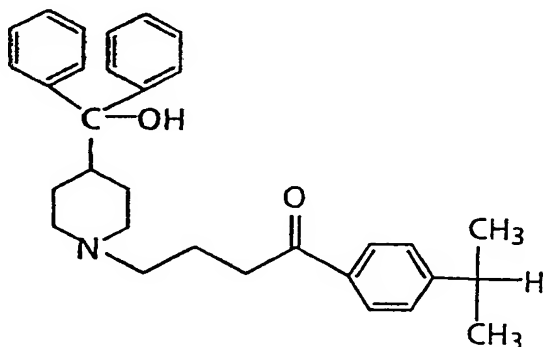
Into a 4L beaker with ice (1kg) and stirring, pour about one-half of the methylene solution above. Stir the mixture for 30 min. Separate the organic and aqueous phases. Wash the organic phase with water (500 mL) and then with an aqueous solution of sodium bicarbonate 1% (500 mL). Work up the other half of the unquenched methylene

chloride solution in a similar fashion. Combine the
5 organic phases and concentrate under vacuum. After
collection of 1.3 L of methylene chloride solution, add
heptane (400 mL) to the residue in order to complete the
10 drying of the isopropyl ketone. Remove the heptane under
vacuum to give a yellow oil. Add methanol (700 mL) to this
oil and store the solution at -20 °C for 16 hours. Separate
15 the formed solids from the supernatant by decantation. Add
hexane (100 mL) and crush the solids in the hexane slurry.
Collect the slurry by suction filtration and wash the
20 filter cake with hexane (300 mL). Dry the filtercake solid
at under vacuum (1 mm Hg, 0.13 kPa) at ambient temperature
to give 1-chloro-4-(4-isopropylphenyl) butanone (561.43 g,
25 73%).

Step 2: 4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-
(4-ISOPROPYLPHENYL) BUTANONE

30

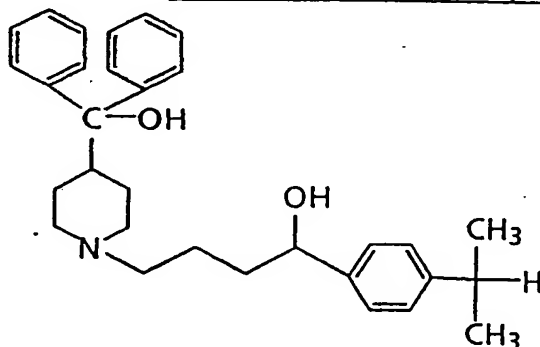
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Stir 4(α,α -diphenyl) piperidine methanol hydrochloride
(131.0 g, 0.43 mol), potassium carbonate (71.3 g, 0.52
mol) and water (200.0 g) in a round-bottomed flask equipped
with a nitrogen bubbler. Add a solution of 1-chloro-4-(4-
isopropylphenyl) butanone (129.3 g, 0.58 mol) in warm
xylenes (70 mL) to the mixture. Add xylenes (70 mL) to
rinse. Heat the mixture to 80 °C for 30 min at 300 RPM then
to 100 °C at 300 RPM for one hour then heat 18 hours at 200
RPM.

Add xylenes (150 mL) and stir the resulting mixture for 2 hours at 92 °C. Allow the mixture to settle and remove the bottom aqueous phase. Wash the organic phase three times with 140 mL each of water, each time heating above 90 °C during the stirring, settling and decanting operations. Remove some of the xylene solvents by distillation at atmospheric pressure, leaving about 180 mL xylenes remaining in the distillation pot. Cool the solution to 40 °C, and add heptane (400 mL). Store the solution at -20 °C for 18 hours to provide a liquid/solid slurry. Collect the solids by suction filtration and wash with heptane (400 mL). Dry the solids under vacuum (1 mm Hg, 0.13 kPa) at ambient temperature to give 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-(4-isoprpylphenyl) butanone as a white powder (179.16 g, 0.39 mol, 91%).

Step 3: 4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-(4-ISOPRPYLPHENYL) BUTANOL



Add 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-(4-isoprpylphenyl) butanone(22.78 g, 50 mmol) to a solution of ethanol/water (126 mL, 90/10). Stir and heat the solution under reflux. Add an aqueous solution of sodium borohydride (12%, 24.4 mmol) and sodium hydroxide (40%). Rinse with additional water (10 mL). Heat under reflux for an additional 25 min after the addition is completed. Add water (84 g) to the refluxing solution. Allow the mixture to cool slowly to ambient temperature. Collect the white solid by suction filtration and wash the filtercake with water at ambient temperature (60 mL) and

water at 92 °C (115 mL). Dry the solids open to air for
5 three days to obtain 21.76 g. Put the resulting compound
(21.00 g) into an erlenmeyer flask with a solution of
ethanol and water (150 mL, 90/10). Heat the solution to
10 reflux and then hot polish filter through fluted filter
paper. Wash the filter paper with hot ethanol water (25 mL,
90/10). Combine the filtrate and transfer to a 500 mL
15 single-neck, round bottomed flask. Heat under reflux. Add
water (36 mL) to obtain some solids. Add absolute ethanol
(30 mL) to the refluxing mixture to obtain dissolution of
20 most of all the solids. Allow the mixture to cool to
ambient temperature and then to ice/water bath temperature.
Collect the resulting white solid by suction filtration,
25 wash the filtercake with ethanol/ water (20 mL, 50/50) and
then with cold ethanol/water (24 mL, 50/50). Dry the
solids overnight open to air to give 17.50 g (77%) of 4-[4-
[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-(4-
isoprpylphenyl) butanol.

30

EXAMPLE 8

4-[4-[4-(HYDROXYDIPHENYLMETHYL)-1-PIPERIDINYL]-1-(4-
ISOPRPYL-3-HYDROXYPHENYL) BUTANOL may be prepared by one
35 ordinary skilled in the art following the above described
example 7 but using 3-isopropyl phenol as starting material
instead of cumene. The hydroxy group may be protected,
more preferably -o-methoxy methyl group is used.

3-Isopropyl phenol is commercially available.

5 The compounds of the present invention are useful as
antihistamines, antiallergy agents and bronchodilators as
more fully described in US patents 4,254,129 issued March
10 3, 1981 and 4,254,130 issued March 3, 1981.

15 The compounds can be administered alone or in the form
of a pharmaceutical composition in combination with
pharmaceutically acceptable carriers or excipients, the
proportion and nature of which are determined by the
20 solubility and chemical properties of the compound
selected, the chosen route of administration, and standard
pharmaceutical practice. The compounds of the invention,
while effective themselves, may be formulated and
25 administered in the form of their pharmaceutically
acceptable acid addition salts for purposes of stability,
convenience of crystallization, increased solubility and
the like.

30 The compounds of this invention can be administered
orally, parenterally, for example, subcutaneously,
intravenously, intramuscularly, intraperitoneally, by
intranasal instillation or by application to mucous
35 membranes, such as, that of the nose, throat and bronchial
tubes, for example, in an aerosol spray containing small
particles of a compound of this invention in a spray or dry
powder form. One skilled in the art of preparing
formulations can readily select the proper form and mode of
administration depending upon the particular
characteristics of the compound selected, the disorder to
be treated, the stage of the disorder, and other relevant
circumstances.

 The compounds of the present invention may be enclosed
in gelatin capsules or compressed into tablets. For the
purpose of oral therapeutic administration, the compounds
may be incorporated with excipients and used in the form of
tablets, troches, capsules, elixirs, suspensions, syrups,

wafers, chewing gums and the like. These preparations
5 should contain at least 4% of the compound of the
invention, the active ingredient, but may be varied
depending upon the particular form and may conveniently be
10 between 4% to about 70% of the weight of the unit. The
amount of the compound present in compositions is such that
a suitable dosage will be obtained. Preferred compositions
15 and preparations according to the present invention are
prepared so that an oral dosage unit form contains between
5.0-300 milligrams of a compound of the invention.

20 The tablets, pills, capsules, troches and the like may
also contain one or more of the following adjuvants:
25 binders such as microcrystalline cellulose, gum tragacanth
or gelatin; excipients such as starch or lactose,
disintegrating agents such as alginic acid, Primogel, corn
starch and the like; lubricants such as magnesium stearate
or Sterotex; glidants such as colloidal silicon dioxide;
30 and sweetening agents such as sucrose or saccharin may be
added or a flavoring agent such as peppermint, methyl
salicylate or orange flavoring. When the dosage unit form
is a capsule, it may contain, in addition to materials of
the above type, a liquid carrier such as polyethylene
35 glycol or a fatty oil. Other dosage unit forms may
contain other various materials which modify the physical
form of the dosage unit, for example, as coatings. Thus,
tablets or pills may be coated with sugar, shellac, or
other enteric coating agents. A syrup may contain, in
addition to the present compounds, sucrose as a sweetening
agent and certain preservatives, dyes and colorings and
flavors. Materials used in preparing these various
compositions should be pharmaceutically pure and non-toxic
in the amounts used.

For the purpose of parenteral therapeutic
administration, including topical administration, the
compounds of the present invention may be incorporated

into a solution or suspension. These preparations should
5 contain at least 0.1% of a compound of the invention, but
may be varied to be between 0.1 and about 50% of the
weight thereof. The amount of the inventive compound
10 present in such compositions is such that a suitable
dosage will be obtained. Preferred compositions and
preparations according to the present invention are
15 prepared so that a parenteral dosage unit contains between
5.0 to 100 milligrams of the compound of the invention.

20 The solutions or suspensions may also include one or
more of the following adjuvants: sterile diluents such as
water for injection, saline solution, fixed oils,
25 polyethylene glycols, glycerine, propylene glycol or other
synthetic solvents; antibacterial agents such as benzyl
alcohol or methyl paraben; antioxidants such as ascorbic
acid or sodium bisulfite; chelating agents such as
ethylene diaminetetraacetic acid; buffers such as
30 acetates, citrates or phosphates and agents for the
adjustment of tonicity such as sodium chloride or
dextrose. The parenteral preparation can be enclosed in
ampules, disposable syringes or multiple dose vials made
of glass or plastic.

35

The quantity of novel compound of formula (I)
administered will vary depending on the patient and the
mode of administration and can be any effective amount.
The quantity of novel compound may vary over a wide range
to provide in a unit dosage an effective amount of from
about 0.01 to 60 mg/kg of body weight of the patient per
day to achieve the desired effect. For example, the
desired antihistamine, antiallergy and bronchodilator
effects can be obtained by consumption of a unit dosage
form such as a tablet containing 1 to 200 mg of a novel
compound of this invention taken 1 to 4 times daily.

For use as aerosols the compounds of this invention in
5 solution or suspension may be packaged in a pressurized
aerosol container together with suitable propellants, for
example hydrocarbon propellants such as propane, butane or
10 isobutane with usual adjuvants as may be necessary or
desirable. The compounds also may be administered in a
non-pressurized form such as in a nebulizer or atomizer.

15 The term patient as used herein is taken to mean warm
blooded animals, birds, and mammals, for example, humans,
20 cats, dogs, horses, sheep, bovine cows, pigs, lambs, rats,
mice and guinea pigs.

25 In another embodiment, the present invention provides
compositions comprising a compound of formula (I) in
admixture or otherwise in association with one or more
inert carriers. These compositions are useful, for
example, as assay standards, as convenient means of making
30 bulk shipments, or as pharmaceutical compositions. An
assayable amount of a compound of formula (I) is an amount
which is readily measurable by standard assay procedures
and techniques as are well known and appreciated by those
skilled in the art.

35 Assayable amounts of a compound of formula (I) will
generally vary from about 0.001% to about 75% of the
composition by weight. Inert carriers can be any material
which does not degrade or otherwise covalently react with a
compound of formula (I). Examples of suitable inert
carriers are water; aqueous buffers, such as those which
are generally useful in High Performance Liquid
Chromatography (HPLC) analysis; organic solvents, such as
acetonitrile, ethyl acetate, hexane and the like; and
pharmaceutically acceptable carriers or excipients.

More particularly, the present invention provides
pharmaceutical compositions comprising an effective amount

of a compound of formula (I) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

10 An effective amount of a compound of formula (I) refers to an amount which is effective, upon single or multiple dose administration to the patient, in providing the
15 desired antihistaminic, antiallergic or bronchodilator effects beyond that expected in the absence of such treatment.

20 An effective amount of a compound of formula (I), such as an effective antiallergic amount, or an effective
25 antihistaminic amount, can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the
30 effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the response of the individual patient; the particular compound administered; the mode of
35 administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

Treating a patient means to prevent or to alleviate the patient's disease or condition.

As it is true for most classes of compounds suitable or use as therapeutic agents certain subclasses and certain specific compounds are more preferred than others. In this instance it is preferred that A is H, and more preferably A is H and R₁ is -CH₃ or -COOH.